IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MEDPOINTE HEALTHCARE INC.,	)	
	)	
Plaintiff,	)	
	)	C. A. No. 06-164 (SLR)
v.	)	
	)	
APOTEX INC. and APOTEX CORP.,	)	
	)	
Defendants.	)	

APOTEX'S RESPONSE TO PLAINTIFF'S MOTION TO STRIKE APOTEX'S JURY DEMAND, STRIKE APOTEX'S AFFIRMATIVE DEFENSE OF UNENFORCEABILITY, DISMISS APOTEX'S COUNTERCLAIM OF UNENFORCEABILITY, AND STRIKE APOTEX'S AFFIRMATIVE DEFENSE OF MISUSE

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

STATUTES

RULES

TREATISES

SUMMARY OF ARGUMENT

MedPointe's motion to strike Apotex's jury demand is premature. Apotex has timely pleaded its jury demand to preserve its right to a jury trial in the event that claims for damages arise prior to resolution of this litigation. MedPointe will have the opportunity to object to Apotex's request in the event the parties are prepared to go to trial and MedPointe has no claims for money damages against Apotex. Because "curtailment of the right to a jury trial should be scrutinized with the utmost care", the Court should deny MedPointe's motion to strike as premature. *Beacon Theatres v. Westover*, 359 U.S. 500, 501 (1959).

MedPointe's motion to strike Apotex's affirmative defenses and dismiss its counterclaims should also be denied. This Court disfavors motions to dismiss affirmative defenses and will not grant a motion to strike "unless it appears to a certainty that … [the movant] would succeed despite any state of facts, which could be proved in support of the defense." *McKesson Information Solutions, LLC v. The Trizetto Group, Inc.*, 2005 U.S. Dist. LEXIS 6733, at *3 (D. Del. Apr. 20, 2005). Apotex's defenses and counterclaims are sufficiently pleaded under the Federal Rules of Civil Procedure to provide MedPointe with fair notice of the nature and substance of Apotex's claims and the defenses and counterclaims allege facts that if proven are cognizable at law. Therefore, MedPointe's motion should be denied in its entirety.

ARGUMENT

I. MEDPOINTE'S MOTION TO STRIKE APOTEX'S JURY DEMAND IS PREMATURE AND SHOULD BE DENIED

Article VII of the United States Constitution provides: "In suits at common law, where the value in controversy shall exceed 20 dollars, the right of trial by jury shall be

preserved." The importance of this constitutional right is reflected in the Federal Rules of Civil Procedure. Fed. R. Civ. P. 38(a) provides that: "The right of trial by jury as declared by the Seventh Amendment to the Constitution or as given by statute of the United States shall be preserved to the parties inviolate." As the Supreme Court stated in *Parsons v. Bedford*, 28 U.S. 433 (1830):

> The trial by jury is justly dear to the American people. It has always been an object of deep interest and solicitude, and every encroachment upon it has been watched with great jealousy.….As soon as the constitution was adopted, this right was secured by the seventh amendment of the constitution proposed by congress; and which received an assent of the people so general, as to establish its importance as a fundamental guarantee of the rights and liberties of the people….

See also Beacon Theatres, 359 U.S. at 501 ("[M]aintenance of the jury as a fact-finding body is of such importance and occupies so firm a place in our history and jurisprudence…any seeming curtailment of the right to a jury trial should be scrutinized with the utmost care.") (quoting *Dimick v. Schiedt*, 293 U.S. 474, 486 (1935); *Chauffeurs, Teamsters and Helpers, Local No. 391 v. Terry*, 494 U.S. 558, 565 (1990)).

The phrase "suits at common law" as used in the seventh amendment "refers to 'suits in which legal rights [are] to be ascertained and determined…'" *Id*. at 564 (quoting *Parsons* v. *Bedford*, 3 Pet. 433, 447 (1830)). To determine whether a particular action will resolve legal rights, and thus come within the Seventh Amendment's guarantee of the right to jury trial, courts examine both the nature of the issues involved and the remedy sought. *Chauffers,* 494 U.S. at 565; *Tull v. United States,* 481 U.S. 412, 417-418 ("First, we compare the statutory action to 18th-century actions brought in the courts of England prior to the merger of the courts of law and equity. Second, we examine the remedy

sought and determine whether it is legal or equitable in nature.") (internal citations omitted)

In the instant case, MedPointe has alleged infringement under § 271(e)(2) and therefore "damages or other monetary relief may be awarded against an infringer only if there has been a commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug." 35 U.S.C. § 271(e)(4)(C). Apotex has not yet engaged in such activities and thus recognizes that at this stage of the proceedings there is no claim for damages. However, Apotex has timely pleaded its jury demand to preserve its constitutional right to a jury trial in the event that claims for damages should arise later in the litigation.

At the present time, pursuant to 21 U.S.C. § 355(j)(4)(B)(iii)(I)-(III), the approval of Apotex's ANDA has been suspended for thirty months, or until the court rules. If a trial takes place after thirty months has expired, Apotex's ANDA may be approved and Apotex would be in a position to begin to manufacture, market or sell Azelastine prior to trial. If this situation arises MedPointe would seek damages and Apotex would be entitled to a jury trial. *See Minnesota Mining and Manufacturing Company v. Alphapharm Pty, Ltd.,* 2002 U.S. Dist. LEXIS 16961, at *9-10 (D. Minn. Mar. 20, 2002) ("In this case, Alphapharm has received approval from the FDA to market its generic, therefore this case has transformed into a typical patent infringement case involving both legal and equitable claims. Accordingly, Alphapharm has a constitutional right to a jury trial with regard to the legal claims raised in its counterclaims.")

While Apotex is interested in seeking a swift resolution of this matter, it is possible that it will be prejudiced in its efforts if the need for discovery from foreign

entities becomes cumbersome and drawn out in Hague Convention procedures. In addition, discovery in this case has not even begun. As discovery develops, Apotex may uncover facts which will require Apotex to seek leave of the Court to amend its answer to include additional counterclaims for anti-trust violations and tortious interference. These additional claims, if alleged, would also entitle Apotex to a jury trial. *See Beacon Theatres*, 359 U.S. at 504; *Curtis v. Loether*, 415 U.S. 189, 196, n.11 (1974); *Lee Pharmaceuticals v. Mishler*, 526 F.2d 1115, 1116 (2d Cir. 1975). MedPointe has not alleged that it would suffer any prejudice if the Court withholds ruling on the jury demand issue until after the parties have had a chance for discovery and have focused and refined their claims (particularly since Apotex's demand is specifically restricted to those claims for which a jury trial would be appropriate). Accordingly, at this stage of the proceedings there is no need for the Court to decide the jury demand issue and MedPointe's motion to strike the jury demand should be denied.[1]

II. MEDPOINTE'S MOTION TO STRIKE APOTEX'S AFFIRMATIVE DEFENSES AND DISMISS ITS COUNTERCLAIMS SHOULD BE DENIED

The law of the Circuit in which the Court resides is applied to motions to dismiss. *Ferguson Beauregard/Logic Controls, Division of Dover Resources, Inc. v. Mega Systems, LLC*, 350 F.3d 1327, 1344 (Fed. Cir. 2003) ("This court reviews the dismissal of a claim under Rule 12(b)(6), a matter of procedure, by applying the law of the regional circuit.")[2] This Court has held that "[m]otions to dismiss affirmative defenses … are disfavored." *McKesson*, 2005 U.S. Dist. LEXIS 6733, *3. In fact, "unless it appears to a

[1] Apotex is concerned claims for damages by MedPointe may begin to accrue after the thirty-month stay has expired if the current action has not been resolved. Apotex therefore respectfully requests in the alternative that if the jury demand is stricken at this time, Apotex be given leave to re-file its jury demand in the event damages begin to accrue.

[2] MedPointe's use of 9th, 5th, and 4th Circuit law is inapposite to its motion to dismiss.

certainty that … [the movant] would succeed despite any state of the facts, which could be proved in support of the defense," this Court prefers not to grant a motion to strike. *Id.* (quoting *Salcer v. Envicon Equities, Corp.*, 744 F.2d 935, 939 (2d Cir. 1984)). The Court applies the same standard with respect to counterclaims. *Item Development AB, Astellas US LLC v. Sicor, Inc.*, 2006 U.S. Dist. LEXIS 15386, *2-3 (D. Del. Mar. 31, 2006) (giving the standard the court applies to a defendant's motion to dismiss plaintiff's claims). Counterclaims must be construed in favor of the œmplainant and the party moving for dismissal has the burden of persuasion. *Id.* (For simplicity, Apotex will be referred to as the "claimant" although it is understood that MedPointe's motion applies to both Apotex's affirmative defenses and corresponding counterclaims).

III. APOTEX'S INEQUITABLE CONDUCT DEFENSE AND COUNTERCLAIMS SATISFY RULE 9(b)PLEADING REQUIREMENTS

Inequitable conduct claims must be pleaded with particularity. *McKesson,* 2005 U.S. Dist. LEXIS 6733; *see also Ferguson Beauregard/Logic Controls, Division of Dover Resources, Inc. v. Mega Systems, LLC*, 350 F.3d 1327, 1344 (Fed. Cir. 2003). The purpose of the Rule 9(b) requirement is to ensure the accused is on notice of the misconduct alleged to constitute inequitable conduct. *See e.g. McKesson,* 2005 U.S. Dist. LEXIS 6733, at *8 (Denying plaintiff's motion to dismiss defendant's inequitable conduct claim because it was "on notice of the misconduct alleged"). The notice requirement is met, for example, where the claimant specifies either "the time, place, and content of any alleged misrepresentations made to the PTO or otherwise give[s] the defendant[ ] notice of the precise misconduct alleged." *Agere Sys. Guardian Corp. v. Proxim, Inc.*, 190 F.Supp.2d 726, 733-34 (D. Del. 2002) (internal quotations omitted). In the appropriate circumstance, "pleadings that disclose the name of the relevant prior art and disclose the

acts of the alleged fraud fulfill the requirements of Rule 9(b)." *McKesson*, 2005 U.S. Dist. LEXIS 6733, at *7-8 (internal quotations omitted).

Apotex has apprised MedPointe of the "time, place, and conduct" alleged to constitute inequitable conduct. Apotex has argued that while prosecuting the application resulting in the '194 patent, the applicant made "affirmative misrepresentation[s] regarding the benefits of azelastine administered as a nasal spray." Answer of Apotex Inc, and Apotex Corp to Plaintiff's Amended Complaint, Affirmative Defenses and Counterclaims ("Apotex's Answer"), at p. 9, 15 (D. I. 11). Specifically, Apotex alleges the applicant's statements that "the azelastine formulations of the '194 patent cause neither somnolence nor the bitter taste side effects of previous azelastine formulations" was a material misrepresentation. Apotex's Answer, at p. 10, 15; *see* U.S. Pat. No. 5,164,194 (Ex. 1 hereto) at col. 1, ln. 63-66 ("It was surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose.") MedPointe now admits in its product insert for Astelin brand azelastine nasal spray that bitter taste and somnolence are major side effects of azelastine formulations. Apotex's Answer at Exhibit A (D. I. 12). While not demonstrative of applicant's knowledge during prosecution of the '194 patent, these admissions provide a strong inference that testing used to support applicant's statements would have revealed these major side effects. However, because discovery in this case has yet to begin Apotex is unable to ascertain what the applicant's test data in fact showed. MedPointe, not Apotex is in the exclusive control of this information. It would be inappropriate for the Court to dismiss Apotex's well founded allegations merely because MedPointe is in the exclusive control of development data necessary for Apotex

to prove its claim. In fact, this Court has held that for similar reasons "[i]n complex litigation, such as cases involving patent infringement, it is through the discovery process that the parties refine and focus their claims" such that motions to dismiss are disfavored. *McKesson*, 2005 U.S. Dist. LEXIS 6733 (refusing to strike affirmative defenses until adequate discovery has been completed).

Apotex's inequitable conduct arguments do not rest alone on the applicant's misrepresentations of the benefits of the azelastine nasal spray formulations. Apotex has also alleged the applicants committed inequitable conduct in seeking to overcome a *prima facie* case of obviousness by comparing the azelastine compound to a prior art compound it knew was not the closest prior art to azelastine.[3] Apotex's Answer at p. 10 ("[D]uring prosecution, the applicant's argued, as an indicium of nonobviousness, that azelastine more effectively inhibited liberation of histamine compared with the prior art, the compound of Example 1 of United States Patent No. 4,704,387 even though Example 4 was closer to azelastine."); *see, e.g.*, Prosecution History of U.S. Pat. No. 5,164,194 (Ex. 2 hereto), Dec. 26, 1989 Request for Reconsideration). It is established law that comparative results submitted to overcome obviousness rejections are material representations. *Norton v. Curtiss*, 433 F.2d 779, 794 (C.C.P.A. 1970) ("Where, as here, an applicant attempts to overcome a rejection by submitting comparative showing of

[3] MedPointe complains that Apotex has "[f]ail[ed] to reference any evidence from the relevant time – *before* the '194 patent issued – that was available to applicants which might contradict statements in the specification or file history[.]" See MedPointe's Motion to Dismiss at p. 22 (emphasis in original) (D. I. 17). MedPointe ignores Apotex's identification of United States Patent No. 4,704,387 as relevant to Apotex's inequitable conduct claims. The '387 patent is indisputably prior art to the '194 patent. In fact, on the cover of the '194 patent the '387 patent is identified as relevant prior art cited during prosecution of the '194 patent. Ex. 1. MedPointe's complaint that Apotex has failed to reference "any evidence from the relevant time" is simply untrue.

properties, the very act of submitting that showing, apart from what is represented therein, must also be regarded as a representation.")[4] An applicant who submits comparative results with compounds that are not the closest prior art to its claimed compound must inform the PTO or be subject to a claim of inequitable conduct. *Id.* This is because in giving comparative results to overcome a rejection "an applicant must be held to be representing that his showing includes a fair and accurate demonstration of the closest prior art of which he is aware." *Id.* at 794. In *Norton*, the C.C.P.A. stated that "[s]ince the most relevant, meaningful comparison would necessarily have to have been between [applicant's claimed product and the closest prior art, applicant's] statements must be considered as an implied representation that, as far as he knew, he was making such a comparison." *Id.* at 796. Applying *Norton* to this case, since the "most relevant, meaningful comparison" would have been between azelastine and the nearest prior art compound, the applicant's comparison between Example 1 of the '384 patent and azelastine was an implied representation that it was comparing azelastine to the nearest prior art. Because applicant's failure to notify the PTO that it was **not** comparing its compound with the closest "most relevant" and "meaningful" prior art, its arguments constitute false misrepresentation giving rise to a claim of inequitable conduct.

Finally, MedPointe admits in its reply to Apotex's counterclaim that it is on notice of specific conduct alleged by Apotex to give rise to a claim of inequitable conduct. In response to Apotex's allegations that it misrepresented the benefits of azelastine nasal spray MedPointe admits specific statements made to the PTO alleged by Apotex to be

[4] C.C.P.A. decisions are binding precedent in this matter. The Federal Circuit has also explicitly approved of *Norton* in *Novelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059 (Fed. Cir. 1998).

material misrepresentations. *See* Corrected Plaintiff's Reply to Defendants' Counterclaims to Amend Complaint ("MedPointe's Reply") at p. 17 (quoting patent) (D. I. 18). These representations were made, at least, as early as November 9, 1988 when the applicants submitted the application resulting in the '194 patent. Ex. 2. MedPointe further admits the date and substance of at least one specific representation alleged by Apotex to be a violation of its duty to inform the PTO that it was not comparing azelastine to the closest prior art. *See* MedPointe's Reply, p. 18 (identifying applicants December 26, 1989 request for reconsideration of an obviousness rejection wherein applicants compared azelastine to Example 1 of the '384 patent). MedPointe also generally admits other instances of alleged misrepresentation. *Id*. at p. 19 ("MedPointe further admits that two declarations relating to these experiments were subsequently submitted to the PTO.") MedPointe therefore admits in its reply to Apotex's counterclaim that it is fully apprised of specific statements made to the PTO, and the relevant dates of the same, giving rise to Apotex's inequitable conduct claims.

Apotex's inequitable conduct allegations are pleaded with particularity sufficient to satisfy Rule 9(b) and put MedPointe on notice of the specific misconduct alleged to constitute inequitable conduct. MedPointe admits as much in its reply to Apotex's counterclaim. MedPointe's motion to dismiss Apotex's allegations of inequitable conduct must therefore be denied.[5]

[5] In the event the Court finds Apotex's allegations infirm in any way, Apotex respectfully requests that the motion be granted without prejudice to Apotex being able to amend its pleadings to provide additional facts, either immediately or as discovery progresses, depending on the nature of the Court's ruling.

IV. MEDPOINTE'S MOTION TO STRIKE APOTEX'S AFFIRMATIVE DEFENSE OF PATENT MISUSE IS PREMATURE AND SHOULD BE DENIED BECAUSE APOTEX'S PLEADING GIVES MEDPOINTE FAIR NOTICE OF ITS DEFENSE

MedPointe's motion to strike Apotex's affirmative defense of patent misuse should be denied because Apotex's pleading gives MedPointe fair notice of its defense and because MedPointe's motion is premature as discovery in this case has not even begun. *See* Charles A. Wright & Arthur R. Miller, Federal Practice and Procedure, §1274 (1990) ("An affirmative defense may be pleaded in general terms and will be held to be sufficient, and therefore invulnerable to a motion to strike, as long as it gives plaintiffs fair notice of the nature of the defense"); *See McKesson*, 2005 U S Dist LEXIS 6733, at *5 (declining to strike defendant's affirmative defense of patent misuse until adequate discovery has been completed).

Apotex's patent misuse defense is premised on MedPointe's bad faith enforcement of a patent it knew or should have known was invalid or unenforceable. To establish patent misuse in this context, the party alleging the misuse must show "a patentee's bad faith in alleging infringement and an anti-competitive effect or purpose behind the allegation." *McKesson*, 2005 U S Dist LEXIS 6733, at *4, n2 (citing *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply*, 45 F.3d 1550, 1558 (Fed. Cir. 1995) and *Advanced Cardiovascular Sys. v. Scimed Sys.*, 1996 U.S. Dist. LEXIS 11702, at *4 (N.D. Cal. July 24, 1996)).

A reasonable opportunity for further investigation or discovery is likely to provide evidentiary support that despite MedPointe's knowledge that U.S. Patent No. 5,164,194 ("'194 patent") was invalid and/or unenforceable, it brought this suit against Apotex in bad faith and for the purpose of maintaining its monopoly over the market for Alezastine

Nasal Spray. This conduct supports a claim of patent misuse which renders MedPointe's patent unenforceable. *Arcade, Inc. v. Minnesota Mining & Mfg. Co*., 1991 U.S. Dist. LEXIS 19768, at * 48 (E.D. Tenn. July 2, 1991) ("Patent misuse occurs when a patentee enforces its patent knowing that it is either invalid or unenforceable or beyond the scope of the patent's legal monopoly."); *Affymetrix, Inc. v. PE Corp*., 219 F. Supp. 2d 390, 397 (S.D.N.Y. 2002); *Amgen, Inc. v. Chugai Pharm. Co*., 706 F. Supp. 94, 105 (D. Mass. 1989), and cases cited therein.

Furthermore, MedPointe's listing of the '194 patent in the F.D.A. orange book forces ANDA applicants to submit a paragraph IV certification. This certification in turn allows MedPointe to bring suit and prohibit the FDA from approving any applications for the listed drug until a judicial resolution of the infringement suit, a judicial determination that the patent is invalid or unenforceable, or thirty months from the patentee's receipt of notice, whichever is earliest. 21 U.S.C. § 355(j)(5)(B)(iii). Discovery is likely to reveal that MedPointe caused the '194 patent to be listed in the orange book with full knowledge of its invalidity and/or unenforceability, thereby illegally restraining trade by prohibiting any competition in the market for azelstine nasal spray. This conduct further supports a finding of patent misuse. *Astra Aktiebolag v. Kremers Urban Dev. Co.*, 2001 U.S. Dist. LEXIS 23879, at *3 (S.D.N.Y. Oct.26, 2001) (Finding allegations that a false FDA certification forced defendants to file a paragraph IV certification sufficient to state a claim of patent misuse).

Patent misuse claims are supported where a court finds "bad faith and improper purpose in bringing the suit, in implementation of an illegal restraint of trade." *Hoffman La Roche Inc. v. Genpharm Inc.*, 50 F. Supp. 2d 367, 379 (D.N.J. 1999) ("Because

Genpharm has alleged that plaintiffs initiated a baseless suit to enforce invalid patents and patents which they knew or should have known were not infringed for anticompetitive purposes to maintain a monopoly over the market for ticlopidine hydrochloride, Genpharm has stated a claim for patent misuse in violation of the Sherman Act, *15 U.S.C. § 2.*") (citing *C.R. Bard Inc. v. M3 Systems, Inc.,* 157 F.3d 1340, 1368 (Fed. Cir. 1998)*;* and *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.,* 45 F.3d 1550, 1558 (Fed. Cir. 1995)). Apotex's patent misuse defense is premised on MedPointe's bad faith enforcement of a patent it knew or should have known was invalid or unenforceable. MedPointe's motion to strike this defense is premature as discovery in this case has not yet begun. A reasonable opportunity for further investigation is likely to provide evidentiary support for Apotex's defense. Apotex's pleading gives MedPointe fair notice. Therefore, MedPointe's motion to strike Apotex's affirmative defense of patent misuse should be denied.[6]

V. MEDPOINTE'S CONDUCT IS NOT PROTECTED BY 35 U.S.C. 271(d)(3) OR NOEER-PENNINGTON

MedPointe asserts that its "commencement of this action cannot constitute patent misuse, as a matter of law…" Plaintiff's Motion to Strike, p. 23. In support of this proposition MedPointe relies on 35 U.S.C. § 271(d)(3). This reliance is misplaced. 35 U.S.C. § 271(d)(3) provides:

> "No patent owner otherwise entitled to relief for infringement or contributory infringement of a patent shall be denied relief or deemed guilty of misuse or illegal extension of the patent right by reason of his having done one or more of the following: . . . (3) sought to enforce his

[6] To the extent that the facts plead with regard to the claims of inequitable conduct and fraud are insufficient, Apotex respectfully requests that the motion be granted without prejudice to Apotex being able to amend its pleadings to provide additional facts, either immediately or as discovery progresses, depending on the nature of the Court's ruling.

> patent rights against infringement or contributory infringement."

35 U.S.C. § 271(d)(3). Thus, this provision generally precludes a finding of patent misuse where a patentee seeks to enforce a valid patent. However, a finding of misuse is precluded **only if** the patent infringement is brought in good faith. *In re Independent Serv. Orgs. Antitrust Litig.*, 964 F. Supp. 1479, 1484 (D. Kan. 1997) (citing *Glaverbel*, 45 F.3d at 1558-59). Thus MedPointe's bad faith enforcement of a patent it knows to be invalid or unenforceable is not protected under 35 U.S.C. § 271(d)(3). Nor is MedPointe's conduct protected under the Noerr-Pennington doctrine. *Hoffman La Roche Inc.*, 50 F. Supp. 2d at 379-380 ("Where a litigant brings a suit for anticompetitive purposes to enforce a patent with the knowledge that the patent is invalid or not infringed, the antitrust immunity of Noerr-Pennington and California Motor Transp. does not apply.") (citing *C.R. Bard, Inc.*, 157 F.3d at 1368).

For the above stated reasons, MedPointe's motion to strike Apotex's affirmative defense of patent misuse should be denied.

CONCLUSION

For the reasons stated herein, MedPointe's Motion to Strike Apotex's Jury Demand, Strike Apotex's Affirmative Defense of Unenforceability, Dismiss Apotex's Counterclaim of Unenforceability, and Strike Apotex's Affirmative Defense of Misuse should be denied.

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Dated: May 18, 2006

732914

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Richard L. Horwitz, hereby certify that on May 18, 2006, the attached document was hand delivered on the following persons and was electronically filed with the Clerk of the Court using CM/ECF which will send notification of such filing(s) to the following and the document is available for viewing and downloading from CM/ECF:

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EXHIBIT 1

US005164194A

United States Patent [19]

Hettche

[11] Patent Number: 5,164,194

[45] Date of Patent: Nov. 17, 1992

[54] AZELASTINE CONTAINING MEDICAMENTS

[75] Inventor: Helmut Hettche, Dietzenbach, Fed. Rep. of Germany

[73] Assignee: Asta Pharma AG, Fed. Rep. of Germany

[21] Appl. No.: 551,644

[22] Filed: Jul. 12, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 268,772, Nov. 9, 1988, abandoned

[30] Foreign Application Priority Data

Nov. 13, 1987 [DE] Fed. Rep. of Germany 3738681

[51] Int. Cl.[5] A61K 9/14; A61K 31/55

[52] U.S. Cl. 424/489; 424/43; 424/45; 424/464; 424/422; 514/212

[58] Field of Search 424/43, 464, 422, 45, 424/489; 514/212; 222/394; 141/24; 239/302; 248/108

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[57] ABSTRACT

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

12 Claims, No Drawings

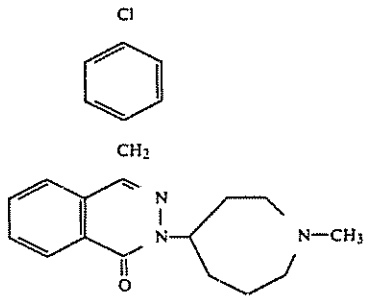
AZELASTINE CONTAINING MEDICAMENTS

This is a continuation of application Ser. No 07/268,72, filed Nov. 9, 1988, now abandoned.

The present invention relates to the treatment of nasal and eye tissues with azelastine.

BACKGROUND OF THE INVENTION

Azelastine is a phthalazinone derivative having the following structural formula:



The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular for prophylactic treatment of asthma. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058.

SUMMARY OF THE INVENTION

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied directly in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste. The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of 1 : 706. This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions. It wa surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.

Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms.

A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissues.

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

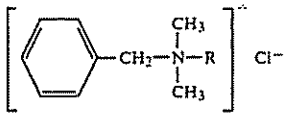
Through the use of nasal drops or a nasal spray, the dosage of azelastine required for the treatment of the cold is lowered approximately tenfold and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or syrups which distribute the active substance throughout the entire body. In the treatment of a banal illness such as a cold, a low incidence of side effects is particularly important and thus represents a considerable medical advance.

Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2- ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preserva-

tives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula C_nH_{2n+1}, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which $R=C_{12}H_{25}$ "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/ volume) of 2-phenylethanol.

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present-as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above. In the case of the eye drops, the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:

thimero sal 0.002–0.02%;

benzalkonium chlorie 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;);

chlorhexidine acetate or gluconate 0.01 to 0.02%;

phenyl mercuric/nitrate, borate, acetate 0.002–0.004%;

p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05–0.15, preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/-weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine components.

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50° to 0.56° C. is attained in comparison to pure water. In Example 1, for instance, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g per 100 ml of solution. The weights given relate in each case to the anhydrous substances

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight-/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide and compressed air.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

When suspensions are used, the maximum particle size of the solid substances (azelastine +auxiliary substances) should not exceed 30 μm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 μm

What occurs is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200,000 parts by weight of carrier substance (0.0005 to 2% of azelastine)

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

EXAMPLE 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient

The following are dissolved, in the following order, into 9.00 kg of water: 10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt. 2 H_2O, 68 g of sodium chloride, 1.25 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogen-phosphate. 12 H_2O as well as 10 g of hydroxypropylmethyl cellulose.)[1]

[1] Commercially available product, for example methocel E4M premium

The solution obtained is diluted to 10.05 kg =10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 μm after careful mixing, the first 500 ml of filtrate being discarded. The filtrate has a pH value of 6.8 ±0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

EXAMPLE 2

Nasal ointment with 0.1% of azelastine hydrochloride

5 kg of polyoxyethylene stearate[2], 8 kg of cetylstearyl alcohol (Lanette 0), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80° C.). Subsequently, a solution heated to 70° C. of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester in 51.021 kg of purified water are emulsified with the aid of a high speed stirrer and the emulsion obtained is stirred until cold and repeatedly homogenized at regular time intervals.

[2] Polyoxyethylene-40-stearate, solid, white to cream-colored mass, D^{25} ca. 1.1, F. 40°–44° C. Solidification point ca. 41° C

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

EXAMPLE 3

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about −55° C. in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at −55° C. 0.0688 kg of micronized azelastine hydrochloride and 0.0688 kg of micron-

ized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about −55° C.

Following closure of the cooling vessel the suspension is again cooled to about −55° C. under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4

Eye drops with 0.05% of azelastine hydrochloride

140 g of polyvinylalcohol (trade name for example: Mowiol 26-88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90° C. and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium dihydrogen phosphate.2 H_2O and 21 g of disodium hydrogen phosphate.2 H_2O in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 μm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.0005 to 2% (weight/-weight) azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 1 in which the medicament contains 0.003 to 0.5% (weight/weight) of azelastine or an amount of a physiologically acceptable salt of azelastine which contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7. A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

12. A method for the treatment of a patient suffering from allergy-related, or vasomotor or rhino-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

PATENT NO.	:	5,164,194
ISSUED	:	November 17, 1992
INVENTOR(S)	:	Helmut Hettche
PATENT OWNER	:	Asta Medica, AG

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

349 days

from November 17, 2009, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 27th day of February 1998.

Bruce A. Lehman

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE EXTENDING PATENT TERM
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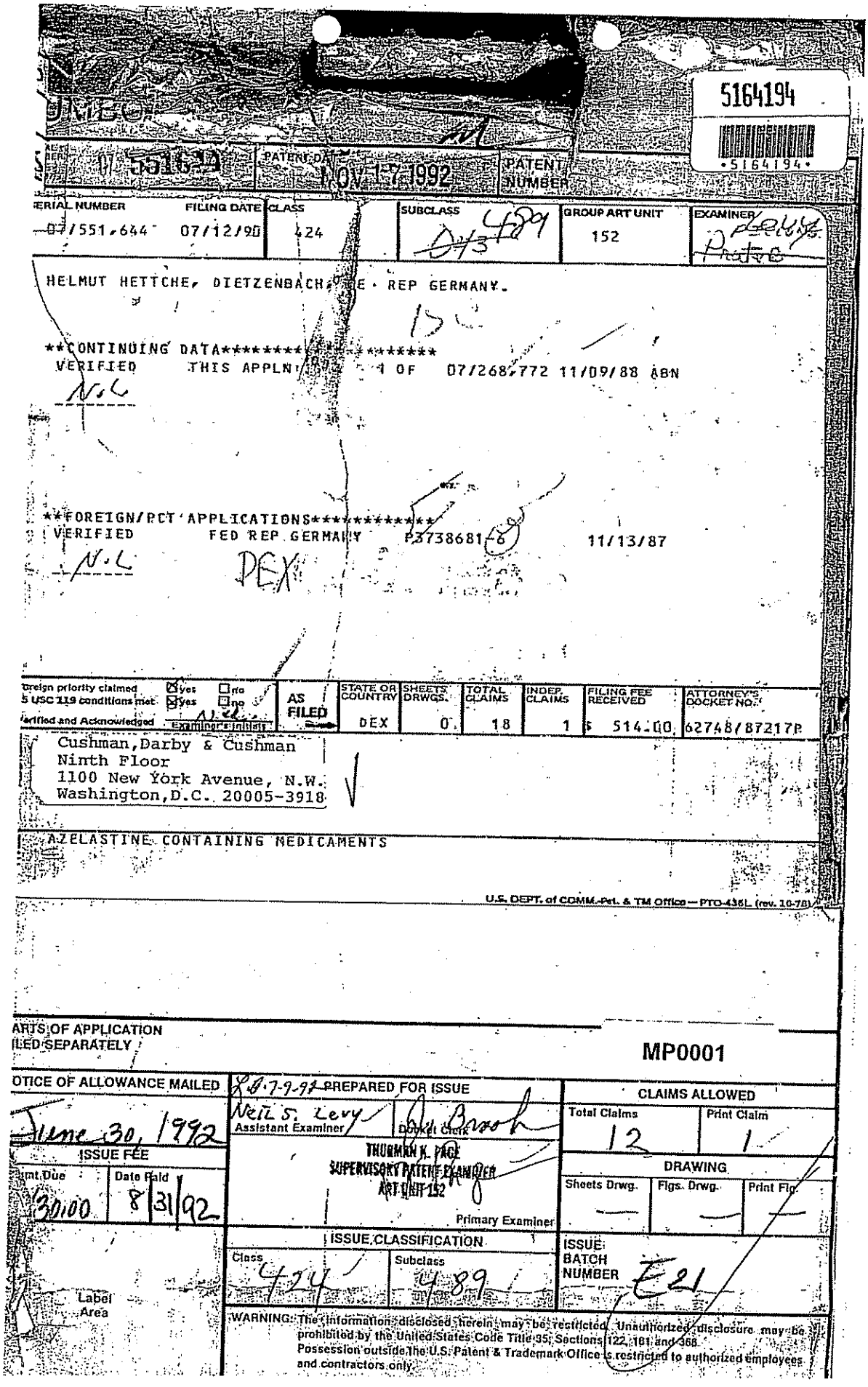
Assistant Secretary of Commerce and
Commissioner of Patents and

EXHIBIT 2



5164194

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PATENT NUMBER 5164194

PATENT DATE NOV 17 1992

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
07/551,644	07/12/90	424	489	152	Page

HELMUT HETTCHE, DIETZENBACH, E. REP GERMANY.

CONTINUING DATA*******
VERIFIED THIS APPLN IS A DIV OF 07/268,772 11/09/88 ABN

FOREIGN/PCT APPLICATIONS********
VERIFIED FED REP GERMANY P3738681.6 11/13/87

DEX

Foreign priority claimed 35 USC 119 conditions met / Verified and Acknowledged	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
☒yes ☐no ☒yes ☐no / Examiner's initials		DEX	0	18	1	$ 514.00	62748/87217P

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Washington, D.C. 20005-3918

AZELASTINE CONTAINING MEDICAMENTS

U.S. DEPT. of COMM.-Pat. & TM Office—PTO-436L (rev. 10-78)

PARTS OF APPLICATION FILED SEPARATELY

MP0001

NOTICE OF ALLOWANCE MAILED June 30, 1992

PREPARED FOR ISSUE 10-7-92

Neil S. Levy, Assistant Examiner

Docket Clerk

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
ART UNIT 152

Primary Examiner

CLAIMS ALLOWED

Total Claims	Print Claim
12	1

ISSUE FEE

Amt Due	Date Paid
1300	8/31/92

DRAWING

Sheets Drwg.	Figs. Drwg.	Print Fig.
—	—	1

ISSUE CLASSIFICATION

Class	Subclass
424	489

ISSUE BATCH NUMBER E21

Label Area

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
REQUEST FOR FILING NATIONAL PATENT APPLICATION WITH SIGNED DECLARATION
(Not for PCT cases)

The Commissioner of Patents and Trademarks
Washington, D.C. 20231

268772

PATENT APPLICATION

Sir:

(Our Deposit Account No. 03-3975
(Our Order No. [redacted]
C# / M#

Herewith is the PATENT APPLICATION of
Inventor(s): HETTICHE, Helmut

Atty. Dkt. 69931 / 87 217 PH
M# / Client Ref.

Title: AZELASTINE CONTAINING MEDICAMENTS

including:

Date: November 9, 1988

1. Specification: 16 pages (only spec. and claims) 2. [ ] Specification in non-English language
3. [x] Declaration [x] Abstract 1 page(s), 18 numbered claims
4. [ ] Drawings: ___ sheet(s) per set: [ ] 1 set informal; [ ] formal of size [ ] A4 [ ] 14"
5. This is a signed [ ] Reissue of USP _____ [ ] CIP [ ] DIV [ ] CONT
[ ] SUBSTITUTE Application (MPEP 201.09) of Serial No. 0 / _____ Filed _____
6. [ ] Attached is an assignment to _____
7. [x] Priority is claimed under 35 USC 119 based on filing in (country) GERMANY
8.

Application No.	Filing Date	Application No.	Filing Date
(1) P37 38 681.6	Nov. 13, 1987	(4)	
(2)		(5)	
(3)		(6)	

9. [ ] (No.) Certified copy (copies) [X] attached; [ ] previously filed (date) _____
in U.S. Application, Serial No. _____, filed on _____
10. [ ] Attached: ___ (No.) Verified Statement(s) establishing "small entity" status under Rules 9 & 27.
11. [ ] Attached:

12. [ ] Preliminary Amendment:

THE FOLLOWING FILING FEE IS BASED ON CLAIMS AS FILED LESS ANY ABOVE CANCELLED

13. Basic Filing Fee ($340.00)						$ 340.00
14. Total Effective Claims	18	minus 20 = *	–	x $12.00	=	+ –
15. Independent Claims	7	minus 3 = *	4	x $34.00	=	+ 136.00
*If answer is zero or less, enter "0"						
16. If any proper multiple dependent claim (ignore improper) is present, add $110.00						+
17.				Subtotal	=	476.00
18. If "small entity" box 10 is X'd, enter half (1/2) of subtotal & subtract						–
19.				TOTAL FILING FEE ENCLOSED	=	$ 476.00
20. If "non-English" box 2 is X'd, add Rule 17(k) processing fee ($26.00)						+
21. If "assignment" box 6 is X'd, add recording fee ($7.00)						+
22. [ ] Attached is a Rule 47 Petition and Petition Fee ($140.00 per Rule 17(h))						+
23.				TOTAL FEE ENCLOSED	=	$ 476.00

The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown in the heading hereof for which purpose a duplicate copy of this sheet is attached. This statement does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed.

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Sig: [signature]
Tel.: 861- 3015

CDC-102 (UTILITY APPLN.) 8/88(1)

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APPLICATION FOR UNITED STATES PATENT

Inventor(s): Helmut Hettche

Invention: AZELASTINE CONTAINING MEDICAMENTS

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SPECIFICATION

26872

ABSTRACT OF THE DISCLOSURE

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

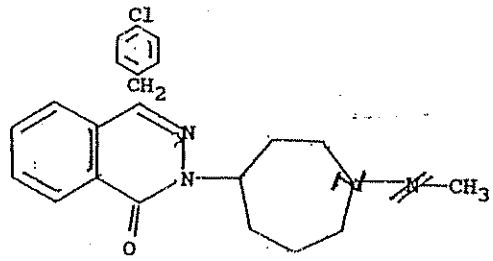
MP0010

AZELASTINE-CONTAINING MEDICAMENTS

The present invention relates to the treatment of nasal and eye tissues with azelastine.

BACKGROUND OF THE INVENTION

Azelastine is a phthalazinone derivative having the following structural formula:



The chemical designation is: 4-(4-chlorobenzyl)-2-(perhydro-1-methyl-azepine-4-yl)-1-(2H)phthalazinone. Azelastine is used in particular for prophylactic treatment of asthma. Azelastine also has anti-allergic and antihistamine properties, see German Patent No. 21 64 058.

SUMMARY OF THE INVENTION

It has now been found that azelastine and its physiologically acceptable salts display particularly advantageous and surprising effects when the corresponding formulations are applied directly in the nose and/or to the conjunctival sac of the eye.

Elimination or marked relief has thus been achieved not only in allergy-related rhinitis, but also in the normal common cold (caused, for example, by rhino viruses) as well as in the vasomotor cold and the symptoms of illness triggered thereby.

It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or relief of reddening of the eye

and of eye irritation) so that the additional use of eye drops is frequently superfluous.

Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy-related conjunctivitis, allergic blepharoedema, catarrhal conditions in the eye or nose, coryza.

Surprisingly, in addition, none of the tiredness that arises with other applications was observed with use according to the invention.

Furthermore the invention provides a way to overcome problems which arise because of azelastine's exceptionally penetrating, bitter taste. The degree of the bitter taste is so intense that it is even found to be unpleasant in a dilution of 1 : ~~106~~ 10^6. This problem has hitherto prevented oral application of azelastine solutions, since patients refuse to take such azelastine solutions or suspensions. It was surprisingly found in trial subjects that this bitter taste was no longer in evidence when the azelastine formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or suspensions of azelastine and its salts nasally without taste impairment. Moreover the bitter taste is barely perceptible when the sprayed azelastine solution or suspension runs down into the pharynx.

Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on azelastine or its salts for the treatment both of the allergy-related and vasomotor-related conditions as well as rhino virus-related cold and its accompanying symptoms.

A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissues.

14/3/88

The preferred embodiment of the invention is a sterile and stable aqueous solution of azelastine or one or more of its salts which can be used in the form of drops, ointments, creams, gels, insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. For example 0.03 to 3 mg of azelastine base should be released per individual actuation.

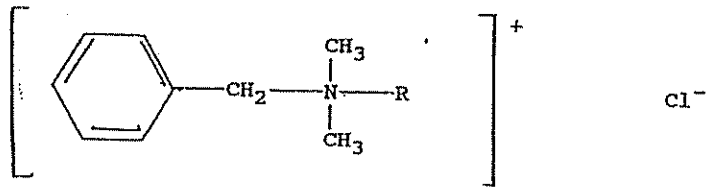
Through the use of nasal drops or a nasal spray, the dosage of azelastine required for the treatment of the cold is lowered approximately tenfold and hence the incidence of the appearance of side effects is considerably lower than in the case of the application of azelastine in orally taken dosage forms such as tablets or ~~juices~~ syrups which distribute the active substance throughout the entire body. In the treatment of a banal illness such as a cold, a low incidence of side effects is particularly important and thus represents a considerable medical advance.

Solvents which may preferably be used for the formulations of the invention are: water, saturated aliphatic mono and polyvalent alcohols which contain 2-3 carbon atoms (for example ethanol, isopropanol, 1,2-propylene glycol, glycerine), liquid polyglycols (molecular weight 200 to 600).

The solvent used is preferably water or mixtures of water with other physiologically acceptable solvents (for example those mentioned above). Preferably, the amount of the latter solvent in the aqueous mixture should not exceed 15% by weight.

MP0013

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2-ethylmercurithio)-benzoate generally known as "thiomersal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]-phenoxy] ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-r-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride". These latter consist of a mixture of the compounds of formula,



in which R represents an alkyl group having the formula C_nH_{2n+1}, wherein n represents a whole number from 8 to 18. The use of a mixture of compounds in which n represents 10 to 14 is particularly preferred and in particular the special compound in which R = $C_{12}H_{25}$. "Benzalkonium chloride" and the compounds of the above formula can be used in concentrations of 0.005 to 0.10, preferably of 0.005 to 0.05, for example of 0.01% (weight/volume for liquid formulations, otherwise weight/weight) and they may optionally be used in combination with 0.2 to 2.0, for example 0.4% (weight/volume) of 2-phenylethanol.

The formulations of the invention (solutions, suspensions as well as oily solutions or suspensions, ointments, emulsions, creams, gels, dosage aerosols) contain 0.0005 to 2, preferably 0.001 to 1, in particular 0.003 to 0.5% (weight/weight) of azelastine (related to the free azelastine base). Should the azelastine be present as a salt, the amounts should be recalculated as necessary to give the amounts of azelastine itself mentioned above. In the case of the eye drops, the same azelastine concentrations apply as in the case of the nasal forms.

In the case of powders, the concentration of azelastine base is 0.0005 to 2 percent by weight related to the solid carrier substances.

In the case of solutions, the dosage per nostril is, for example, 0.01 to 0.2 ml, in particular 0.05 to 0.15 ml. Such a dosage should be applied once to several times, preferably 1 to 5 times daily (optionally also hourly).

In the case of use at the eye (eye drops) the dosage is for example 1 drop (about 0.05 ml) of the solution or corresponding amounts of the semi-solid formulation forms.

Possible acid components for azelastine salts are, for example: hydrohalic acids (HCl, HBr), sulphuric acid, phosphoric acids (H_3PO_4, metaphosphoric acid, polyphosphoric acids), nitric acid, organic mono-, di- or tricarboxylic acids of aliphatic, alicyclic, aromatic or heterocyclic organic acids (embonic acid, citric acid, tartaric acid), aliphatic and aromatic sulfonic acids (for example camphorsulfonic acid).

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is between 0.001 to 0.10, preferably 0.01 g per 100 ml of solution/suspension or 100 g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used:

thiomersal 0.002 - 0.02%;

benzalkonium chloride 0.002 to 0.02% (in combination with thiomersal the amount of thiomersal is, for example = 0.002 to 0.005%;);

chlorhexidine acetate or gluconate 0.01 to 0.02%;

phenyl mercuric nitrate, borate, acetate 0.002 - 0.004%;

p-hydroxybenzoic acid ester (for example a mixture of the methyl ester and propyl ester 7 : 3): 0.05 - 0.15, preferably 0.1%.

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The preservative used is preferably a combination of edetic acid (for example as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is used in a concentration of 0.05 to 0.1%, benzalkonium chloride being used in a concentration of 0.005 to 0.05%, preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine components.

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal

secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50 to 0.56°C is attained in comparison to pure water. In Example 1, for instance, such substances would be used in such an amount which is iso-osmotic with 68 g of sodium chloride (0.68%).

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example:

Glucose $1H_2O$ 3.81 g ; saccharose 6.35 g ; glycerine 2.2 g; 1,2-propylene glycol 1.617 g ; sorbitol 3.84 g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

10

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It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 6 to 7.5, preferably 6.5 to 7.1.

The amount of citric acid is, for example, 0.01 to 0.14, preferably 0.04 to 0.05 g, the amount of disodium hydrogenphosphate 0.1 to 0.5, preferably 0.2 to 0.3 g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The sub-

sequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide and compressed air.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

When suspensions are used, the maximum particle size of the solid substances (azelastine + auxiliary substances) should not exceed 30 µm.

In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 µm.

What occurs is, for example, a vaporizing of solid azelastine or its salts. In this case the azelastine or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate. The concentration of azelastine is 1 part by weight of azelastine to 50 to 200,000 parts by weight of carrier substance (0.0005 to 2% of azelastine).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

Example 1

Nasal spray or nasal drops or eye drops with 0.1% azelastine hydrochloride as active ingredient:

The following are dissolved, in the following order, into 9.00 kg of water:

10 g of azelastine hydrochloride, 5 g of edetic acid disodium salt. 2 H_2O, 68 g of sodium chloride, 1.25 g of alkylbenzyldimethylammonium chloride (benzalkonium chloride), 4.38 g of citric acid, 64.8 g of sodium monohydrogenphosphate.12 H_2O as well as 10 g of hydroxypropylmethyl cellulose.)[1]

The solution obtained is diluted to 10.05 kg = 10 liters with water. The solution is filtered through a membrane filter of pore size 0.2 µm after careful mixing, the first 500 ml of filtrate being discarded. The filtrate has a pH value of 6.8 ±0.3. This is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles which are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.14 ml of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride are sprayed into the nose per actuation in the form of the solution.

If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

1 Commercially available product, for example methocel E4M premium.

MP0021

Example 2

Nasal ointment with 0.1% of azelastine hydrochloride:

5 kg of polyoxyethylene stearate[2], 8 kg of cetylstearyl alcohol (Lanette O), 20 kg of white Vaseline, 15 kg of liquid paraffin and 0.5 kg of silicon oil are melted together in a heatable vessel. 126 g of p-hydroxybenzoic acid methyl ester and 53 g of p-hydroxybenzoic acid propyl ester are dissolved in the melt (temperature of the melt 80°C). Subsequently, a solution heated to 70°C of 0.1 kg of azelastine hydrochloride, 140 g of p-hydroxybenzoic acid methyl ester and 60 g of p-hydroxybenzoic acid propyl ester are emulsified into 51.021 kg of purified water with the aid of a high speed stirrer and the emulsion obtained is stirred until cold and repeatedly homogenized at regular time intervals.

The ointment is filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

Example 3:

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride per stroke:

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane are cooled to about -55°C in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at -55°C. 0.0688 kg of micronized azelastine

2 Polyoxyethylene-40-stearate, solid, white to cream-colored mass, $D.^{25}$ ca. 1.1, F. 40-44°C. Solidification point ca. 41°C.

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hydrochloride and 0.0688 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about -55°C.

Following closure of the cooling vessel the suspension is again cooled to about -55°C under intensive stirring. It is then ready to be filled.

With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 0.5 mg of azelastine hydrochloride. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

Example 4:

Eye drops with 0.05% of azelastine hydrochloride.

140 g of polyvinylalcohol (trade name for example: Mowiol 26 - 88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection purposes, the suspension is heated to 90°C and left at this temperature for 45 minutes. After cooling, the solution obtained is mixed with the following solutions:

5 g of azelastine hydrochloride in 1 liter of water for injection purposes, 0.2 g of phenyl mercury ~~silver~~ nitrate in 2 liters of water for injection purposes, 70 g of sodium chloride in 1 liter of water for injection purposes.

The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide solution, mixed with a solution of 15 g of sodium hydrogen phosphate.2 H_2O and 21 g of disodium hydrogen phosphate.2 H_2O in 1 liter of water for injection purposes and filled up to 10 liters with water for injection purposes.

Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 µm with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

What is claimed is:

16

What is claimed is:

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eye a medicament which contains a member of the group consisting of azelastine and its physiologically acceptable salts.

2. A method as set forth in claim 1 in which the medicament contains 0.0005 to 2% (weight/weight) of azelastine.

3. A method as set forth in claim 2 in which the medicament contains 0.001 to 1% (weight/weight) azelastine.

4. A method as set forth in claim 3 in which the medicament contains 0.003 to 0.5% (weight/weight) azelastine.

5. A method as set forth in claim 1 in which the medicament contains a pharmaceutically usable preservative in an amount of 0.001 to 0.1%.

6. A method as set forth in claim 1 in which the medicament is a solution.

7. A method as set forth in claim 1 in which the medicament is an aqueous solution.

8. A method as set forth in claim 1 in which the medicament is a solution which contains 0.001 to 0.05% (weight/volume of solution) of sodium-2-(ethylmercurithio)-benzoate or 0.001 to 0.1% (weight/volume of solution) of alkylbenzyldimethyl ammonium chloride.

9. A method as set forth in claim 1 in which the medicament is applied by spraying.

10. A method as set forth in claim 1 in which the medicament is applied as drops.

11. A method as set forth in claim 1 in which the medicament is a powder.

19

MP0025

12. A method of treating a patient suffering from allergy-related, or vasomotor or rhino virus-related colds or symptoms which comprises applying directly to the patient's nasal tissues or to the conjunctival sac of the patient's eye a medicament which contains a member of the group consisting of azelastine and its physiologically acceptable salts.

13. A dispensing container containing an eye dropper, said container also containing a solution of azelastine or a physiologically acceptable salt of azelastine.

14. An atomizing container having a pump sprayer, said container containing a solution of azelastine or a physiologically acceptable salt of azelastine.

15. A compressed gas atomizing container having a valve constructed and arranged to release a predetermined amount of a atomized liquid upon each actuation, said container containing a propellant and a solution (or suspension) of azelastine or a physiologically acceptable salt of azelastine.

16. A compressed gas atomizing container as set forth in claim 15 in which the concentration of azelastine or a physiologically acceptable salt of azelastine is such that 0.03 to 3 mg of azelastine is released upon each actuation of said valve.

17. A dispensing tube containing an ointment, said ointment containing azelastine or a physiologically acceptable salt of azelastine.

18. Powder containing 0,0005 to 2% of azelastine or a physiologically acceptable salt of azelastine as active agent together with conventional pharmaceutical carrier substances.

11/3/88

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re PATENT Application of

Helmut HETTCHE

Serial No. 07/268,772 Group Art Unit: 158

Filed: November 9, 1988 Examiner: P. Prater

For: AZELASTINE - CONTAINING MEDICAMENTS

December 26, 1989

* * * * *

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

The applicant respectfully requests reconsideration of the rejection of claims 1-18 in the Office Action dated June 23, 1989.

The basis of the rejection is that the Examiner considers the claimed method, composition and articles to be prima facie obvious from the disclosure of Engel et al patent 4,704,387 in view of four secondary references. Engel et al discloses compounds whose structures are similar to that of the presently claimed azelastine, differing in the R group. In the Engel patent, R is benzyl, phenethyl, methoxyethyl or allyl, whereas, in the present invention, the corresponding group is methyl. Barnes, Ashkenaz, Mendl and Arp are cited in connection with dependent claims 13-17, but are not understood to add to the relevance of Engel et al to applicant's method claims.

While the process of applicant's claims 1-12 may be prima facie obvious, that process is not obvious because it produces an unobvious result. Applicants have conducted comparative experiment which demonstrate this advantage. Regrettably, the results of these experiments have come to

hand only a few days ago, and so there has not been sufficient time to obtain a declaration. Therefore, the data is presented below. We will submit a declaration as soon as it can be obtained, after the Christmas holiday season.

The experiments are based on the fact that an allergic reaction in the eyes or the nose results from the liberation of histamine from mast cells as a result of the action of an antigen. The liberated histamine causes rhinitis symptoms.

The effectiveness of azelastine in preventing these symptoms in the eyes and the nose can be determined by measuring its effectiveness in preventing the liberation of histamine from sensitized rat peritoneal mast cells. The mast cells are incubated first with a test substance and then challenged with antigen. The amount of histamine released is measured, and this is compared with the total potential release of histamine. The amount of inhibition of histamine release is calculated for each test substance.

In the case of azelastine, the inhibition was 47.1% whereas, in the case of the compound of Example 1 of the cited Engel patent, the inhibition was only 24.4%.

Thus, azelastine was about twice as effective as the compound of Example 1 of the Engel patent. This result is surprising and unexpected.

For this reason, it is submitted that the claimed process is unobvious.

In regard to claims 13-17, the Examiner cites In re Durden 763 F.2d 1406 (Fed.Cir. 1985), but that case is not thought to be relevant to the present case. In Durden, the court dealt with the obviousness of a process of making a novel compound, using a starting material which had not previously been used for that process. The process itself was

known. The court held that the process was obvious, but it cautioned against using its decision as precedent in other situations:

> We reiterate another principle followed in obviousness issue cases, which is to decide each case on the basis of its own particular fact situation. What we or our predecessors may have said in discussing different fact situations is not to be taken as having universal application.

The present case involves, in the case of claims 13-17, various forms of apparatus for dispensing azelastine into nasal or eye tissues. This is a different fact situation from the Durden case. For the reason given in the quoted passage, we submit that Durden does not deal with the patentability of this type of claim.

Furthermore, in Durden, the Court distinguished the fact situation from that in In re Kuehl, 475 F.2d 658 (C.C.P.A. 1973) where the result of the process was not foreseeable. In the present case, where there is evidence of a surprising result, it is submitted that the holding of Durden is not applicable, for the same reason as that which distinguished Durden from Kuehl.

The Kuehl case is much more relevant to the present case than Durden. The question in Kuehl was whether it was obvious to use a new zeolite in a catalytic process which had been used previously with other zeolites. The Court held that prior cases, relating to the obviousness of using a known process of making a new substance, were not relevant to that question. Further, the Court held that it was appropriate to consider the surprising result which was achieved with the new zeolite:

> We note that in the present case the novel catalyst, ZK-22, is not merely itself reduced but itself catalyzes the

> hydrocarbon charge in the claimed process, a result that was not predictable until appellant had made his invention.

In the present case, the claimed articles produce a result which was not foreseeable from the teachings of the prior art, and, therefore, it is submitted that the articles of claims 13-17 are patentable.

Favorable reconsideration and allowance are respectfully requested.

The applicants have informed us that the following documents have been cited in counterparts of the present application:

German Application:

Published German Patent Application DE-OS 21 64 058, corresponding to U.S. Patent 3,813,384

Arzneimittel, Fortschritte 1972-1985, Pages 936 and 939 (1977)

Org.-Chem. drugs and their symptoms, Vol. III,m No. 6496 (1987)

European Application:

German Patent Application 3 530 793, corresponding to U.S. Patent 4,704,387.

Copies of these documents are attached.

Respectfully submitted,

CUSHMAN, DARBY & CUSHMAN

By Lawrence A. Hymo

Lawrence A. Hymo

Reg. No. 19,057